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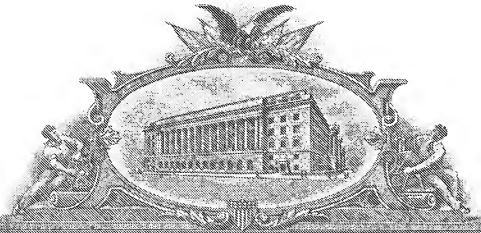

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)

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Additional inventors are being named on the 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

DOSAGE FORM CONTAINING AMORPHOUS DRUG SUBSTANCE

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☐ Application Data Sheet. See 37 CFR 1.76

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☐ Applicant claims small entity status. See 37 CFR 1.27.

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[Page 1 of 2]

Respectfully submitted,

SIGNATURE

Date August 9, 2004

REGISTRATION NO. 28,605 *(if appropriate)*

Docket Number: GEN 3.8-014

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Docket Number GEN 3.8-014

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Docket No. GEN 3.8-014

DOSAGE FORM CONTAINING AMORPHOUS DRUG SUBSTANCE

INTRODUCTION TO THE INVENTION

The present invention relates to a solid pharmaceutical dosage form for oral administration, containing an amorphous drug substance.

Amorphous materials have properties that can be of advantage in the preparation of solid dosage forms, such as improved solubility, bioavailability, functional mechanics, and adhesivity. However, the increased reactivity of an amorphous solid, with a consequent high propensity to spontaneous transform to the crystalline state under certain conditions, such as relative humidity, applied force and temperature, may negatively affect the physical and chemical stability of their pharmaceutical preparations. Thus, the use of drugs and excipients in amorphous form represents both potential advantages and disadvantages to the formulator. Attempts have therefore been made to overcome the disadvantages by modulating the solid-state reactivity of amorphous substances, in terms of increasing or decreasing their reactivity. The various approaches used for the formulation of an amorphous material involve the use of dry granulation techniques for tableting, complexation, dry mixing, melt extrusion, co-precipitation, spray drying, co-milling, and others.

Retaining the drug in an amorphous form in the final dosage form generally improves the dissolution characteristics of the dosage form. A poster by S. E. Bartsch et al., "Melt Granulation of Solid Dispersions – Granulation Mechanism, Tableting and Dissolution Behavior," presented at the 17th Congress of the Austrian Pharmaceutical Society, April 24-26, 2003, Graz, Austria, indicates that dissolution rates increase in the following order: pure drug substance < physical mixture < solid dispersion < melt granules < amorphous drug < tableted melt granules. This study compared tablets, made from glibenclamide granules produced by fluid-bed melt granulation, that used different granule sizes and were formed by different

compression forces (between 10 and 20 kN), and found higher dissolution rates when the granules were larger, and when the compression forces were higher.

The various methods of producing an amorphous form of compounds include: spray drying; freeze drying (lyophilization); melt precipitation; vapor condensation; crash cooling from supercritical fluids, e.g. using Solution Enhanced Dispersion by Supercritical fluids (SEDS), Rapid Expansion of Supercritical Solution (RESS) processes, etc.; co-precipitation with suitable excipients such as sugars, acids, polymers, insoluble or enteric polymers, or surfactants to form solid dispersions; and molecular dispersions, co-precipitates or co-evaporates by melting or fusion, or from solvents including supercritical solvents.

It is known that amorphous materials frequently exhibit improved compression characteristics over the corresponding crystalline forms. For example, commercial grades of lactose are produced by a spray drying technique to introduce some amorphous content, which improves the compression force and hardness profiles of this tablet excipient. (A. H. Kibbe, Ed., *Handbook of Pharmaceutical Excipients, 3rd Edition*, American Pharmaceutical Association, Washington, D.C. USA, p. 276, 2000)

Amorphous materials do not exhibit the three-dimensional long-range order that is found in crystalline materials, but are structurally more similar to liquids where the arrangement of molecules is random. Amorphous solids are not crystalline and therefore do not give a definitive X-ray diffraction pattern. In addition they do not give rise to a melting point and tend to liquefy at some point beyond the glass transition point (B. C. Hancock and G. Zografi, "Characteristics and Significance of the Amorphous State in Pharmaceutical Systems," *Journal of Pharmaceutical Science*, Vol. 86, pp. 1-12, 1997)

While the amorphous form of the drug has distinct physicochemical properties, it frequently has a persistent stability problem, in terms of maintaining its amorphous form during storage. Often the crystalline form of the drug has a lower free energy and thus, over time, the amorphous drug will tend to crystallize. The rate of crystallization may be influenced by storage conditions, such as temperature and humidity, as well as by the other constituents of the composition.

In the manufacture of drug substances, or in the processing of pharmaceutical solids, degrees of disorder through the formation of defects and amorphous regions are often observed. The amorphous state is mostly detected after lyophilization, spray drying, or milling. It results in a higher energy state than that for the crystalline state. This can provide more advantageous properties such as enhanced dissolution rate or better tableting properties. Often it is associated with increased chemical instability and difficulties in mixing and milling. Solid-state transformation upon storage is the most common and undesirable property since the driving force is kinetic, which is often difficult to suppress. Furthermore, depending on the conditions, metastable or stable forms may result. Amorphous forms are more hygroscopic and absorbed water plays the role of plasticizer, causing a lowering of the glass transition temperatures, resulting in an accelerated process of crystallization. The form of the eventual crystal is highly unpredictable. The change of the form of the drug substance affects the quality of the drug product, in terms of inconsistencies in the purity, identity and bioavailability of the drug product. Attempts have been made in the past to overcome these problems.

Published U.S. Patent Application 2003/0104063 A1 (Babcock et al.) teaches a pharmaceutical composition comprising a dispersion of a low-solubility drug and a matrix, combined with a concentration-enhancing polymer. At least a major portion of the drug is amorphous in the dispersion. The compositions improve the stability of the drug in the dispersion, and/or the bioavailability of the drug.

Published U.S. Patent Application 2003/0129250 A1 (Batycky et al.) reports an improved dissolution of poorly soluble drugs without sacrificing targeted flowability, wetability, selective agglomeration, annealing, yield or polymorphic stability. This is achieved by forming particles for oral drug delivery by spray drying a dilute solution of the poorly soluble drug and excipients. The particles comprise regions of poorly soluble drug wherein the dissolution rate enhancement is between about 2-fold and about 25-fold higher than that of the drug in bulk form.

It is still desired to obtain a composition comprising an amorphous drug that is physically and/or chemically stable under typical storage conditions, can be formed via practical processing conditions, and that has an enhanced bioavailability. These

needs, and others that will become apparent to one of ordinary skill in the art, are met by the present invention, which is described in detail below.

SUMMARY OF THE INVENTION

In one aspect, the invention includes a method of preparing a pharmaceutical dosage form, comprising: (a) forming a mixture comprising a drug that is substantially amorphous and pharmaceutically acceptable excipients; and (b) applying a pressure between about 0.2 and 5 tons to form minitablets.

In another aspect, the invention includes a method of preparing a pharmaceutical dosage form, comprising: (a) forming a mixture comprising a drug that is substantially amorphous and pharmaceutically acceptable excipients; (b) applying a pressure between about 0.2 and 5 tons to form minitablets; and (c) applying a coating to the minitablets.

In other aspects, the pressure applied to form minitablets is between about 0.2 and 3 tons, or between about 0.2 and 1 ton, or about 0.5 ton.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphical depiction of the results of the experiment in Example 2.

Figure 2 is an X-ray powder diffraction pattern for crystalline esomeprazole magnesium trihydrate.

Figure 3 is an X-ray powder diffraction pattern for amorphous esomeprazole magnesium trihydrate.

Figure 4 is an X-ray powder diffraction pattern of tablets prepared according to Example 1.

DETAILED DESCRIPTION OF THE INVENTION

The term "substantially amorphous" in the context of this invention means that the substance has no greater than about 10 percent by weight crystalline content.

The content which is crystalline can easily be determined by X-ray powder diffraction techniques, as is known in the art.

Fig. 2 is the X-ray powder diffraction pattern, using Cu K_α radiation, of crystalline esomeprazole magnesium trihydrate. Fig. 3 is the X-ray powder diffraction pattern, using Cu K_α radiation, of amorphous esomeprazole magnesium trihydrate. In each instance, the x-axis is 2θ, in degrees, and the y-axis is intensity. Using this analytical technique, it is possible to detect about 2 percent by weight of crystalline content in an amorphous material sample.

The art is replete with reports of conversion of the amorphous form of a substance to crystalline form during conventional tableting procedures, and in the presence of moisture. The present inventors in their attempt to formulate several amorphous drug substances have discovered that an amorphous drug substance, upon undergoing wet granulation, drug layering through coating, or compression in conventional tablet compression equipment, has shown changes in form from amorphous to crystalline. The presence of crystalline drug in a final dosage form affects its dissolution, when compared to a dosage form containing the pure amorphous form of the drug.

The invention can also be applied to crystalline forms of a drug, which are susceptible to polymorphic conversion to a different crystalline form. Some of these drugs are vanlaxafine and donepezil.

The invention can be applied to any of the amorphous drugs that are susceptible to conversion to a crystalline form during processing or during storage. Examples of such drugs are omeprazole, esomeprazole magnesium trihydrate, atorvastatin, and clopidogrel.

But, surprisingly, the inventors have found that minitablets produced by the use of a reduced compression pressure do not show a significant change from the amorphous form of the drug.

Minitablets are inexpensive to produce and also save time and provide flexibility in designing dosage forms. Minitablets, which are for purposes of this application tablets of any shape having a maximum dimension smaller than 3 mm, are an interesting alternative in producing multiple-unit dosage forms. They are

made by ordinary tableting machines by direct compression, and have several advantages because of their production process and their product properties.

Minitablets show a resistance against densification and can be compressed to graded relative densities at reduced pressures. This increased densification under pressure leads to both higher permanent densification and higher elastic densification, which in turn results in higher elastic recovery. The inventors discovered that by using a compression pressure of only about 0.2 to 5 tons, preferably about 0.2 to 3 tons, more preferably about 0.2 to 1 ton, and most preferably about 0.5 ton, to produce tablets having diameters of about 1 mm to 3 mm, they were able to avoid the conversion of the amorphous drug substances into crystalline forms. It was also observed that the minitablets also have reduced capping tendency when compared to conventional tablets.

The unit "ton" as used herein means kilonewtons (kN). This is consistent with usage of the term by manufacturers of tablet compression machinery, and is a unit of force that is applied to the material being compressed with a punch and die.

The minitablets have moreover been shown to have several additional advantages over the conventional tablets. One advantage of minitablets lies in their precision of size, resulting in a high degree of dosage precision. Each individual minitablet meets all the requirements of a single-dose drug form, such as uniformity of mass and content. They can therefore also be used individually.

Useful formulations using the invention are as shown in the examples, which are presented to demonstrate certain aspects of the invention, but are not intended to limit the scope of the invention, as it is defined in the appended claims.

EXAMPLE 1

A dosage form containing either 40 or 20 mg of esomeprazole was prepared as follows:

Ingredients	mg for 40 mg Dose	mg for 20 mg Dose
Core		
Esomeprazole magnesium trihydrate	44.5	22.3
Mannitol	242	264.2
Low-substituted hydroxypropyl cellulose	17.5	17.5
Magnesium oxide	20	20
Sodium lauryl sulfate	7	7
Colloidal silicon dioxide	3.5	3.5
Sodium stearyl fumarate	17.5	17.5
Total	352	352
Subcoat		
Zein F 6000	12	12
Eudragit™ L 100-55	1.9	1.9
Triethyl citrate	0.19	0.19
Cum. Total	366.09	366.09
Enteric coat		
Eudragit™ L 100-55	80.27	80.27
Triethyl citrate	8.06	8.06
Glyceryl monostearate	1.6	1.6
Titanium dioxide	1.6	1.6
Cum. Total	457.62	457.62

Minitablets were produced by mixing all of the core ingredients, and the dry mixture was directly compressed into cylindrical tablets having the diameter 2.5 mm, height 1.6-1.9 mm, and average weight 11 mg. The minitablets were then sub-coated with a solution of zein, triethyl citrate, and Eudragit™ L 100-55 (a copolymer of methacrylic acid and methyl methacrylate, sold by Röhm America LLC,

Piscataway, New Jersey USA) in isopropanol and water, and dried. Next, coated minitablets were enteric-coated using a solution of Eudragit™ L 100-55, glyceryl monostearate, and triethyl citrate in isopropanol, the solution containing suspended titanium dioxide, and dried. The enteric-coated minitablets were then filled into hard gelatin capsules. About 44 to 46 minitablets were contained in each capsule.

An uncoated compressed core was crushed and analyzed by X-ray powder diffraction, using Cu K_α radiation. The pattern is shown as Fig. 4.

EXAMPLE 2

Tablets prepared according to the preceding example were tested to determine the dissolution characteristics, using the procedure in Method 711 of *United States Pharmacopeia 24*, The United States Pharmacopeial Convention, Inc., Rockville, Maryland USA, 1999. As a comparison, tablets were similarly prepared using crystalline esomeprazole magnesium trihydrate.

The tablets were immersed in a pH 6.8 phosphate buffer solution at 37°C and the solution stirred constantly during the test period. At intervals, samples of the solution were taken for analysis of the drug content. Release of the drug from the tablets into solution is shown in the following table:

Time, minutes	Percent Drug Released	
	Crystalline	Amorphous
0	0	0
10	15	14
20	35	54
30	53	86
45	70	91

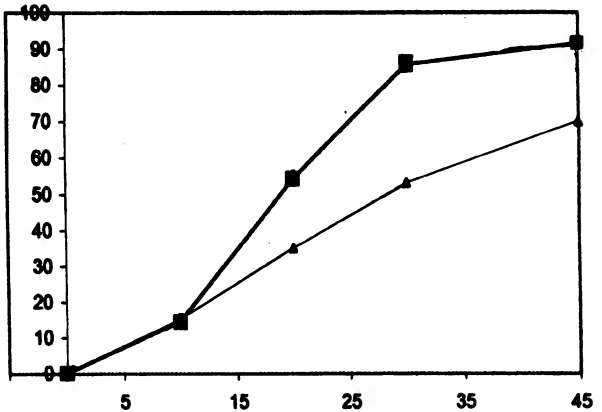

FIG. 1

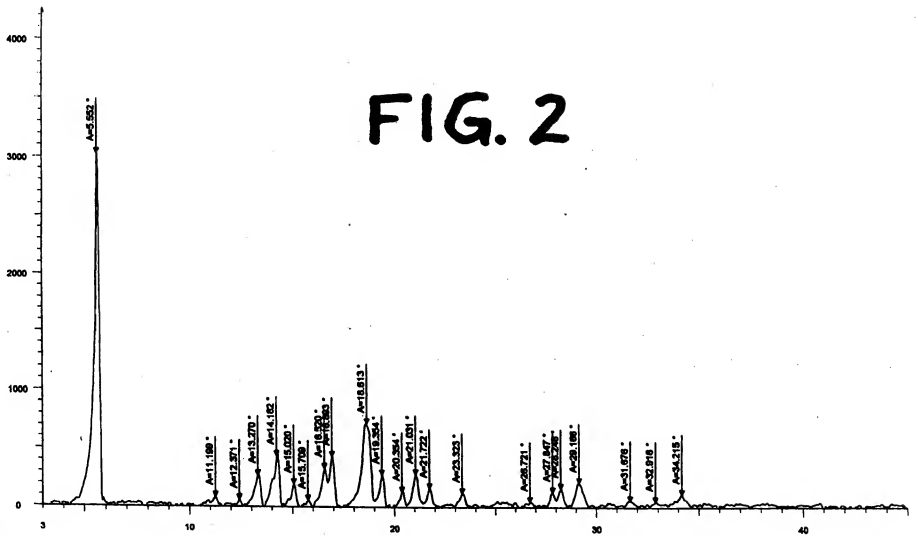

FIG. 2

FIG. 3

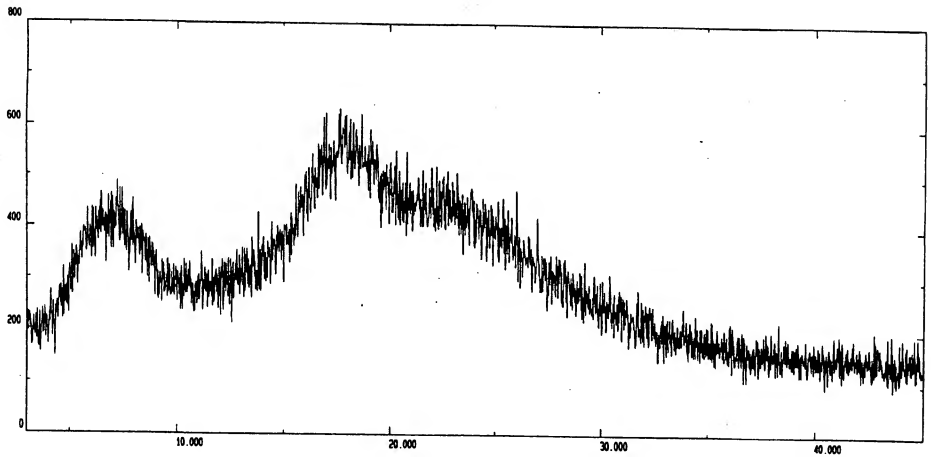

FIG. 4